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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/648,593	08/26/2003	Fei Huang	D0273 NP	5265

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EXAMINER	
SWOPE, SHERIDAN	
ART UNIT	**PAPER NUMBER**
1652	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/19/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/648,593	HUANG ET AL.	
	Examiner	Art Unit	
	Sheridan L. Swope	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41-51* is/are pending in the application.

4a) Of the above claim(s) *42-51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *100206;101006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1652.

Applicant's response, on September 14, 2006 to the First Action on the Merits of this case mailed March 14, 2006, is acknowledged. It is acknowledged that applicants have cancelled Claim 52 and amended Claim 41. Claims 41-51 are pending.

In support of their request that the Restriction/Election requirement be withdrawn, Applicants provide the following arguments.

(A) Claim 41 is not a generic claim and Claims 42-51 are not species claims of a genus. Claim 41 refers to measurement of at least one informative gene, EphA2, while Claims 42-51 add the additional informative genes.

(B) Since Claims 42-51 contain the limitation of Claim 41, measurement of EphA2, examining Claims 42-51 would require no additional searching.

(C) Since the claims contain overlapping subject matter, restriction is improper (MPEP 806.04).

These arguments are not found to be persuasive for the following reasons.

(A) Reply: It is acknowledged that Claim 41 is not a generic claim. As explained in the Restriction/Election requirement, Inventions I-VI are independent because the methods of Inventions I-VI comprise different steps, utilize different products and/or produce different results. Thus, each specific combination of informative genes represents a different product to be used in the recited method.

(B) Reply: It is acknowledged that, if Claim 41 was allowable, Claims 42-51 would require no additional search of the prior art. However, even if Claim was allowable, Claims 42-51 would require additional examination under 35 USC 101 and 112. Moreover, Claim 41 is not currently allowable and thus, examination of Claims 42-51 would require additional search of the prior art as well as examination under 35 USC 101 and 112.

(C) Reply: The Inventions I(A)-(ZZZ...) are distinct inventions because they are physically and functionally distinct products.

Claims 42-51 were previously withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Claim 41 is hereby reconsidered.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Double Patenting

Provisional rejection of Claim 41 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claim 16 of US Application 11/072,175, for the reasons set forth in the prior action, is maintained.

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement

Rejection of Claim 41 under 35 U.S.C. 112, first paragraph lack of enablement, for the reasons explained in the prior action, is maintained. In support of their request that said rejection be withdrawn, Applicants provide the following arguments.

(D) The specification demonstrates that the 137 predictor polynucleotides of Table 2 as well as the 40, 15, and 7 predictor sets of Tables 2, 4, and 5, respectively, can predict the sensitivity of breast cancer cells to an inhibitor of Src class kinases as well as other protein tyrosine kinases. The 1.131 Declaration filed September 14, 2006 provides further evidence that said predictor sets are useful for predicting the sensitivity to additional protein tyrosine kinase inhibitors.

(E) Applicants disagree with the Office's assertion that the structure of BMS-A must be disclosed in order for the skilled artisan to make and use the recited invention.

(F) The elected invention is not directed to compositions of matter directed to a genus of protein tyrosine kinase inhibitors. Thus, whether the skilled artisan is able to make and use the recited method is not dependent on whether the specification teaches the structure of protein tyrosine kinase inhibitors and how said inhibitors may be modified.

(G) Any type of breast cancer cell can be used in the recited invention because the object of the invention is to determine which cells are sensitive to specific tyrosine kinase inhibitors.

(H) Neither Woll et al nor Fernandez-Trigo et al are relevant to the instant invention.

These arguments are not found to be persuasive for the following reasons.

(D) Reply: The elected invention is directed to using the EphA2 gene as a predictor for responsiveness of breast cancer cells to protein tyrosine kinase inhibitors. Therefore, results using the predictor sets of Tables 2, 4, and 5 as well as those described in Applicants' declaration are only relevant in as far as they describe the use of the EphA2 gene as a predictor. It is acknowledged, based on the use of BMS-A, as described in the specification, and PP1, as described for the rejection of Claim 41 under 35 USC 103(a), that the skilled artisan is enabled for using the EphA2 gene as a predictor for determining which breast cancer cells will be sensitive to inhibitors of Src-class kinases. However, the specification fails to enable the skilled artisan to use the EphA2 gene as a predictor for determining which breast cancer cells will be sensitive to inhibitors of BCR-ABL, PDGF-R, c-Kit, EphA1, or EphA2 kinases, as recited in amended Claim 41.

(E) Reply: It is acknowledged that the structure of BMS-A need not be disclosed in order for the skilled artisan to make and use the recited invention.

(F) Reply: This basis for the instant rejection, guidance on the structure of the encompassed kinase inhibitors, is withdrawn.

(G) Reply: It is acknowledged that it is improper to reject Claim 41 under 35 USC 112, first paragraph, because the type of breast cancer cell that can be used is not disclosed. This basis for the instant rejection is withdrawn.

(H) Reply: Woll et al and Fernandez-Trigo et al teach what is well known in the art, that determining successful treatment methods for cancer is unpredictable.

For these reasons and those set forth in the prior action, rejection of Claim 41 under 35 U.S.C. 112, first paragraph lack of enablement, is maintained.

Written Description

Rejection of Claim 41 under 35 U.S.C. 112, first paragraph/insufficient written description, for the reasons explained in the prior action, is maintained. In support of their request that said rejection be withdrawn, Applicants provide the following arguments.

The claimed methods are not a "genus of methods" requiring the teaching of a number of "representative species". The claimed invention is merely directed to a method of predicting whether a breast cancer cell is sensitive to a protein tyrosine kinase inhibitor. The specification demonstrates that the predictor set of Table 2, 4, and 5 can predict the sensitivity of breast cancer cells to inhibitors of Src-class kinases as well as inhibitors of BCR-ABL, PDGF-R, c-Kit, EphA1, or EphA2 kinases. The 1.131 Declaration filed September 14, 2006 provides further evidence that said predictor sets are useful for predicting the sensitivity to a additional protein tyrosine kinase inhibitors.

These arguments are not found to be persuasive for the following reasons. Again, the elected invention is directed to using the EphA2 gene as a predictor for responsiveness of breast cancer cells to protein tyrosine kinase inhibitors. The specification (Table 4) and prior art describe use of the EphA2 gene as a predictor for determining which breast cancer cells will be sensitive to inhibitors of Src-class kinases. However, the specification fails to describe, in a manner that conveys that the inventors had possession of the elected invention, a method for using the EphA2 gene as a predictor for determining which breast cancer cells will be sensitive to inhibitors of BCR-ABL, PDGF-R, c-Kit, EphA1, or EphA2 kinases, as recited in amended Claim 41.

For these reasons and those set forth in the prior action, rejection of Claim 41 under 35 U.S.C. 112, first paragraph lack insufficient written description, is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Rejection of Claim 41 under 35 U.S.C. 103(a) as being unpatentable over Kassenbrock et al, 2002 in view of Wang et al, 2002 and further in view of Ogawa et al, 2000, for the reasons stated in the prior action, is maintained.

In support of their request that said rejection be withdrawn, Applicants provide the following arguments.

(I) For a rejection under 35 USC 103(a) to be proper, the combined references must teach or suggest all claim limitation. None of the instant references teach a method for predicting whether a breast cancer cell will be resistant or sensitive to a protein tyrosine kinase inhibitor by measuring the expression level of the EphA2 receptor.

(J) The Examiner's logic in combining the instant references is in error and contrary to the teachings of the cited publications. (i) Kassenbrock et al do not teach that the effect of PP1 to inhibit Cbl phosphorylation would have an antagonistic effect on EphA2. (ii) In fact, Wang et al teach the opposite: that Cbl phosphorylation would be expected to increase EphA2 activity, since Cbl phosphorylation is vital to its function. Specifically, Wang et al teach that the N-terminal TKB domain plays a critical role in the association of Cbl with

activated RTKs, as well as their negative regulation. That, phosphorylation of Cbl is essential for its association and inhibition of EphA2. And that, when Cbl activity was diminished, a dose-dependent increase in levels of EphA2 was seen. (iii) Kassenbrock et al also teach that activation of Cbl is dependent on its phosphorylation. Accordingly, the art teaches against the Examiner's argument that inhibition of Cbl by PP1 would be expected to lead to inhibition of EphA2.

(K) In the interest of prosecution, Claim 41 has been amended to recite a tyrosine kinase inhibitor of one or more of Src, Fgr, Fyn, Yes, Blk, Hck, Lck, Lyn, BCR-ABL, PDGFR, c-Kit, EphA1, and EphA2.

These arguments are not found to be persuasive for the following reasons. It is acknowledged that

(I) Reply: It is acknowledged that, for a rejection under 35 USC 103(a) to be proper, the combined references must teach or suggest all claim limitation. However, it is not required that any one of the instant references teach a method for predicting whether a breast cancer cell will be resistant or sensitive to a protein tyrosine kinase inhibitor by measuring the expression level of the EphA2 receptor. If any of the instant references did teach said method, this would be a rejection under 35 USC 102.

(J) Reply: (i) Because this is a rejection under 35 USC 103(a), not 102, it is not necessary for Kassenbrock et al to teach that the effect of PP1 to inhibit Cbl phosphorylation would have an antagonistic effect on EphA2. (ii) It is acknowledged that the teachings of Wang et al are that phosphorylation of Cbl is essential for its association and inhibition of EphA2. Therefore, inhibition of Cbl phosphorylation by PP1 would be expected to increase expression of

EphA2. Claim 41 recites a method using a kinase inhibitor wherein sensitivity to the inhibitor is reflected in an increased expression of EphA2. Therefore, the teachings of Wang et al are consistent with the instant rejection of Claim 41. (iii) See (ii) above.

(K) Reply: Since PP1 is an inhibitor of Src-class kinases, said amendment does not overcome the instant rejection.

Applicant's amendment necessitated any new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Regarding filing an Appeal, Applicants are referred to the Official Gazette Notice published July 12, 2005 describing the Pre-Appeal Brief Review Program.

Final Comments

To insure that each document is properly filed in the electronic file wrapper, it is requested that each of amendments to the specification, amendments to the claims, Applicants'

remarks, requests for extension of time, and any other distinct papers be submitted on separate pages.

It is also requested that Applicants identify support, within the original application, for any amendments to the claims and specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 571-272-0943. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published application may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on the access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Sheridan Lee Swope, Ph.D.
Art Unit 1652

SHERIDAN SWOPE, PH.D.
PRIMARY EXAMINER